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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/788,650	02/27/2004	Chaitan Khosla	300622000205	7286

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EXAMINER

CHEN, STACY BROWN

ART UNIT	PAPER NUMBER
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1648

DATE MAILED: 07/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/788,650

Applicant(s)

KHOSLA ET AL.

Examiner

Stacy B. Chen

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 September 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-22 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-22 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 27 February 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 11/5/04; 1/6/05.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

1. This application has been transferred to examiner Stacy Chen, Art Unit 1648.

Applicant's amendment filed September 23, 2005 is acknowledged. The Office regrets the delay in responding to the amendment. Claims 1-22 remain pending and under examination. Upon consideration of the claims, new grounds of rejection are set forth below.

2. The terminal disclaimers filed on 9/23/2004 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US Patents 6,080,555 and 6,750,040 have been reviewed and are accepted. The terminal disclaimer has been recorded. Therefore, the rejection of claims 1-16 under the judicially created doctrine of obviousness-type double patenting is withdrawn. However, additional obviousness-type double patenting exists with regard to Applicant's other patents (see below).

Specification

3. The application is objected to because of alterations which have not been initialed and/or dated as is required by 37 CFR 1.52(c). Applicant is requested to verify if the alteration on page 63, line 10, was made by Applicant. The alteration in the scanned application is "see ex. 10". If Applicant made the change, a properly executed oath or declaration which complies with 37 CFR 1.67(a) and identifies the application by application number and filing date is required. If Applicant did not make the alteration, this objection will be withdrawn. Further, the first paragraph of the specification needs to be updated to reflect the current status of all related patent applications.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7 and 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. It is apparent that *S. coelicolor* strain CH999 is required to practice the claimed invention because it is a necessary limitation for the success of the invention as stated in the claims. As a required element it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification, or otherwise readily available to the public. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of *S. coelicolor* strain CH999. See 37 CFR 1.802. One cannot practice the claimed invention without the strain. Therefore, access to *S. coelicolor* strain CH999 is required to practice the invention. The specification does not provide a repeatable method for the exact *S. coelicolor* strain CH999 without access to *S. coelicolor* strain CH999 and it does not appear to be readily available material.

Deposit of *S. coelicolor* strain CH999 in a recognized deposit facility would satisfy the enablement requirements of 35 U.S.C. 112., because the strains would be readily available to the public to practice the invention claimed, see 37 CFR 1.801- 37 CFR 1.809.

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If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

- (a) during the pendency of this application, access to the invention will be afforded to one determined by the Commissioner to be entitled thereto;
- (b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon granting of the patent;
- (c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;
- (d) a viability statement in accordance with the provisions of 37 CFR 1.807; and
- (e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803 - 37 CFR 1.809 for additional explanation of these requirements.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kao *et al.* (*Science*, 1994, 265:509-512, "Kao") in view of Donadio *et al.* (*PNAS USA*, 1993, 90:7119-7123, "Donadio (1993)") and Donadio *et al.* (*Gene*, 1992, 115:97-103, "Donadio (1992)").

The claims are drawn to a modified functional modular polyketide synthase (PKS) system, or a functional portion thereof, said function portion comprising at least two modules, of said PKS, wherein said PKS has been modified to prevent its utilization of its native starter unit, but wherein said PKS is able to incorporate a diketide substrate into a polyketide that is at least a triketide. The PKS system is contained in a host cell, specifically wherein the host cell is heterologous to said modified PKS. The host cell is a *Streptomyces* host cell. The host cell is permeable to the diketide substrate. The host cell is modified to delete a native PKS contained in said cell. The host cell is *S. coelicolor* CH999. The diketide substrate is formed by coupling a starter unit (acetyl CoA, malonamyl CoA, for example) with an extender unit (malonyl Co-A, for

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example). The diketide substrate is in the form of an N-acetyl cysteamine (NAc) thioester, specifically, (2S,3R)-2-methyl-3-hydrozypentanoyl-NAc thioester.

Kao teaches the biosynthesis of a polyketide using a modified functional modular PKS that is expressed within a heterologous host cell, *i.e.*, *Streptomyces* CH999 (abstract, page 510, column 1, first full paragraph, and page 511, second column last paragraph). The polyketides are synthesized from precursors supplied externally to the cells (see Figures 1 and 2, and page 510, second column). Kao also teaches that the advantage of heterologous expression from the cloned gene allows manipulation of that gene providing a powerful model for the rational design and engineered biosynthesis of polyketides through genetic manipulation (page 509, column 2). In addition, Kao teaches a relaxed specificity of the PKS modules for start unit moiety and illustrate the ability of downstream active sites to utilize growing acyl chains with different starter units (page 511, first column, first full paragraph). Kao does not teach using a PKS which specifically is modified so as to prevent utilization of the native starter unit for the modular PKS thus inhibiting the initial step in the chain elongation and initiation from a natural or endogenous starter unit, but instead, supplying an intermediate starter unit in order to force the synthesis of a particular polyketide from this supplied unit.

Donadio (1993), however, teaches that polyketide synthesis can be reprogrammed by abolishing various activities resulting in the production of novel complete macrolides (page 7119, second column, first full paragraph). This shows that the individual units of the PKS module can be modified with the singular result of changes in the ultimate structure of the product macrolide. Further, Donadio (1992) suggests a rational design strategy for macrolide structures involving alterations in the composition of the synthetic units and in particular the

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starter units can be replaced (abstract and pages 100-101, bridging paragraph). Thus, a general picture emerges of a system that can be manipulated at several levels, resulting in the final product. Thus it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Kao, due to the added flexibility with regard to engineering the final product of this PKS system. Therefore, one of ordinary skill in the art would have been motivated to do so since it would allow the steering of the synthesis toward desired products from exogenously supplied starter units without concomitant contamination with products initiated from native starter units. One would have had a reasonable expectation of success that such a system would have worked because both of Donadio alter the PKS, resulting in various polyketide products (abstract). With regard to the diketide substrates being N-acetyl cysteamine (NAc) thioester, specifically, (2S,3R)-2-methyl-3-hydrozypentanoyl-NAc thioester, the use of either of these would have been obvious. One would have been motivated to use these substrates in the course of optimization. Therefore, the claims are rejected over Kao, in view of Donadio (1993) and Donadio (1992).

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Double Patenting

6. Claims 12-22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of prior U.S. Patent No. 6,274,560 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims are a species of the instantly claimed genus. A species obviates a genus. Therefore, a terminal disclaimer is required in order to overcome this rejection.

7. Claims 12-22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of prior U.S. Patent No. 6,531,299 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims are a species of the instantly claimed genus. A species obviates a genus. Therefore, a terminal disclaimer is required in order to overcome this rejection.

Conclusion

8. No claim is allowed. *This action is non-final because of the new grounds of rejection set forth.* Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James C. Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

A handwritten signature in black ink that reads "Stacy B. Chen". The signature is written in a cursive, flowing style.

Stacy B. Chen
July 15, 2005